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Pathomorphological Characteristics of Trophoblast and Serum Human Chorionic Gonadotropin Levels in Diagnosis of Partial Hydatidiform

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ABSTRACT

Introduction: Partial molar trophoblast degeneration is a benign disease characterised by numerous complications such as an invasive mole and malignant alteration.

Methods: This was a retrospective study which recruited 70 pregnant women diagnosed with hydatidiform mole or with physiological pregnancy spontaneously aborted. The pregnant women had similar demographic features and were included in two groups. 35 pregnant women with a molar pregnancy diagnosed during the first trimester were included in the study group; while 35 pregnant women with miscarriages during the first trimester were included in the control group.

Results: Examined trophoblast changes were: type of atypia, amount and mass of trophoblast proliferation. Specific β HCG serum levels were observed in all pregnant women before the treatment. Pregnant women in the study group had statistically significant higher levels of β HCG serum in comparison with the control group (both average levels 60191.37±49662.75 and levels according to gestational age). Statistically significant changes of villous trophoblast were observed by the pathomorphological analysis: mild trophoblast atypia (57.14%); pronounced trophoblast mass (45.71%) and mild trophoblast proliferation amount (51.43%).

Conclusion: Serum β-HCG level measurements and pathomorphological analysis of chorionic villi are reliable and effective methods in a partial mole diagnostics.

Keywords: partial hydatidiform mole, trophoblast, serum β-HCG levels

INTRODUCTION

Hydatidiform mole is a condition characterized by trophoblast tissue altered into numerous and almost transparent vesicles of various size partially or completely replacing normal chorionic villi. Pathologically changed villi are interconnected by thin but strong layers of connective tissue so macroscopically the placenta appears as fish roe-like or as clusters that resemble grapes – hydatidiform mole (1).

Based on differences in morphology, histopathology, karyotype and clinical features, hydatidiform mole can be categorized into partial and complete

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moles. A complete mole (55%-75% of all molar pregnancies) is characterized by hydropically degenerated villi, absence of embryo and amniotic sac. A partial mole (25%-45% of all molar pregnancies) is characterized by a partial degeneration of villi while trophoblast proliferation is focally pronounced (2).

Hydatidiform mole incidence varies from 0.5 to 8.3 per 1000 live born children and is significantly different across countries. The incidence of molar pregnancy in Asia is seven to ten folds higher than in the countries of North America and Europe (3). Statistically, 290 cases of pathological trophoblast a year per 300 000 births and miscarriages were reported in Croatia (4). 1.5 cases of the gestational trophoblastic disease per 1000 births was reported during a seven-year-period at the Department of Gynaecology and Obstetrics, Clinical Centre Serbia (5). In our country, however, the incidence of gestational trophoblastic disease cannot be precisely reported since there is neither a register of disease nor a disease specific program and management protocol.

Since β HCG is synthesized in syncytiotrophoblast, it is a significant indicator of its functional condition. Due to trophoblast proliferation, ever present in molar chorionic villi, β HCG titer is increased although absolute titer value by itself is not a reliable evidence of hydatidiform mole presence (1).

Normal trophoblast differentiation and function during an implantation and placentation are of great importance for a successful pregnancy, while disorders in those processes contribute to development of numerous pathologic pregnancies including the gestational trophoblast disease (6). Abnormal trophoblast hyperplasia is a requirement for the diagnosis of molar pregnancy (7). In practice, it has been observed that correlation between histological appearance of mole and its clinical course has not been constant and absolute. The well differentiated mole can have a malignant course while anaplastic mole can be innocent (8).

According to recent studies, most of the authors found numerous complications in molar pregnancy (9). Molar pregnancies are considered as premalignant lesions since they can be malignantly altered. Approximately 15%-25% of mole develops into an invasive mole and 3%-5% into choriocarcinoma (10). The gestational choriocarcinoma is preceded by a hydatidiform mole in 30% to 60% patients which is 1000 times higher than after a normal pregnancy (8).

The aim of this study was to investigate the importance of determining serum human chorionic gonadotropin levels as well as the importance of pathomorphologic analysis of trophoblast changes as a source of β HCG with a goal of using those methods in diagnostics.

Participants and Methods

This was a retrospective study which included 70 pregnant women diagnosed with hydatidiform mole or with physiological pregnancies spontaneously aborted. Based on survey results and a patient's file, diagnostic test data were processed while findings were pathohistologically verified at the Department of Pathology, UCC Tuzla. The pregnant women were reported to have almost similar demographic characteristics and were included in two groups.

35 pregnant women with a molar pregnancy diagnosed during the first trimester treated by evacuating the molar tissue by uterine suction or curettage were included in the study group.

35 pregnant women with physiological pregnancy spontaneously aborted during the first trimester treated by uterine suction or curettage were included in the control group.

Molar pregnancy diagnosis was suggested by detailed patient history; gynaecological and ultrasound examination; serum β HCG level and pathohistological tissue verification after an evacuation of the uterine cavity.

Inclusion criteria: 1) singleton pregnancy, 2) gestational age until the 12th week (the first trimester), 3) reliable gestational age (exact date of the last menstrual period, early ultrasound examination), 4) molar pregnancy diagnosis, 5) physiological pregnancy terminated by miscarriage due to cervical insufficiency.

Specific serum β HCG levels were noticed in all pregnant women (study and control group) before a pregnancy termination, which were determined by a quantitative β HCG assay (the Architect total β HCG) using ARCHITECT CI 800. Blood samples were extracted from a cubital vein according to a standard procedure. Available data were compared with reference values for a gestational age (11).

Conception tissue obtained after the suction curettage of the cavum uteri was fixed in buffered formaldehyde solution (pH 7.2-7.4), paraffin embedded,

while 4μm tick histological sections were stained by haematoxylin and eosin method to examine the basic light-microscopic morphological characteristics.

Statistical analysis

Derived values were processed by standard statistical methods such as calculation of mean and standard deviation or median and interquartal range depending on data distribution. The chi-square test was used for determining differences in distribution of cross-section qualitative variable (independent distribution). ANOVA was used to test equality of arithmetic mean of quantitative variable and a factor. The results are shown in tables and graphs but also in clear written presentation with numerical analysis.

Standard level of significance $p<0.05$ was chosen as the statistical significance and non-parametric statistical tests the Mann Whitney test, X^2 test and Fisher test were also used for evaluation.

RESULTS

Serum β HCG Values

The average β HCG levels are shown in Table 1 and Figure 1. The average β HCG levels in the study group was 60191.37 mIU/L and in the control group 2021.76 mIU/L.

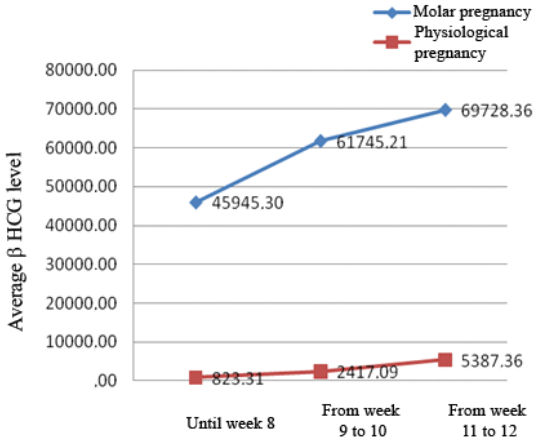

FIGURE 1. Average β HCG levels in the groups according to a gestational age

Based on the standard level of significance $p< 0.05$ with the risk of 5%, it can be concluded that there was a statistically significant difference in the average β HCG levels between the groups. Therefore, the higher average β HCG level was recorded in the study group.

TABLE 1. Difference in average β HCG levels between groups

Observed Characteristics	Hydatidiform Mole	Physiological Pregnancy	df1	df2	F	p
	μ ± σ	μ ± σ				
Serum β HCG value	60191.37 ±49662.75	2021.76 ±2974.73	1	68	47.846	0.000

TABLE 2. Number and Characteristics of Pregnant Women according to Pathomorphologic Trophoblast Characteristics

Observed characteristics		Molar Pregnancy (35)				
		F	%	Chi square	Df	P
Types of Atypia	Moderate	10	28.57	10.00	2	0.0070
	Mild	20	57.14			
	Pronounced	5	14.29			
	Total	35	100.00			
Trophoblast Proliferation Mass	Moderate	10	28.57	2.46	2	0.2930
	Mild	9	25.71			
	Pronounced	16	45.71			
	Total	35	100.00			
Trophoblast Proliferation Amount	Moderate	18	51.43	12.40	2	0.0020
	Mild	15	42.86			
	Pronounced	3	8.57			
	Total	35	100.00			

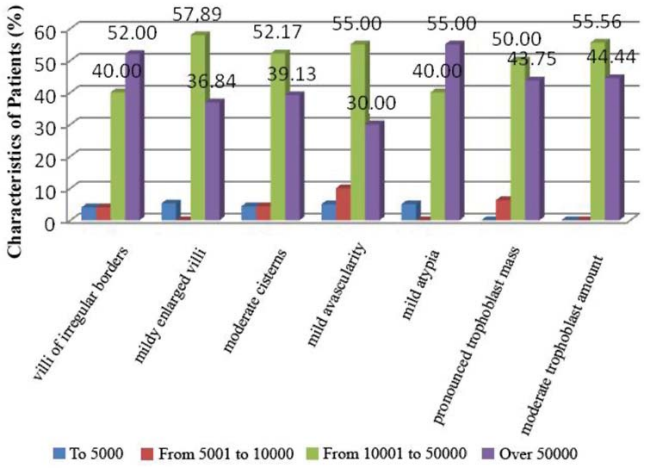

FIGURE 2. Relationship between the most significant pathomorphological changes and β HCG levels

Significantly higher β HCG levels were recorded in pregnant women with hydatidiform mole at all gestational ages.

Pathomorphological Characteristics of Trophoblast

Microscopic characteristics of trophoblastic chorionic villi in partial mole were examined following the molar pregnancy guidelines according to Genest (12). Pathomorphological characteristics were present only in the study group.

The results of examination of types of atypia, mass and amount of trophoblast proliferation are shown in Table 2.

The prevalence of mild atypia was observed in 57,14% of cases, analyzing the trophoblast atypia incidence. Statistically significant difference in proportional prevalence of individual types of trophoblast proliferation mass was not observed. The most prevalent was the pronounced trophoblast proliferation mass in 45.71% of cases. Examining the amount of villi affected by trophoblast proliferation, the moderate trophoblast proliferation amount was observed in 51.43%, which was significantly higher in contrast to the mild trophoblast proliferation amount 42.86%.

The Figure 2 illustrates that among the most significant histopathological villous changes in partial hydatidiform mole more than 1/2 cases had high β HCG levels.

DISCUSSION

The most important part of routine preoperative diagnostic screening of molar pregnancy is a quantitative HCG level measurement as well as measurement of its subunit β. The hyperplastic trophoblastic epithelium, either normal or atypical, produces increased β HCG levels. The levels exceed those recorded in an early pregnancy and are substantially above 50000 IU. The upper limit of β HCG values is not determined and can amount to several hundred thousand IU/L (13). The β HCG secretion is proportional to the amount of viable trophoblast (14). The literature suggests to variability in β HCG levels in molar pregnancy. Genest et al. (15) pointed to the preevacuation β HCG level over 100000 IU in 46% cases. Menczer (16) reported that 30 (41%) of 74 patients with molar pregnancy showed the preevacuation β HCG level over 100000 IU. The present study results suggest that the average β HCG serum level in patients with molar pregnancy was 60191.37 ± 49662,75 which was statistically significantly higher in comparison with normal pregnancy (2021.76 ± 2974.73). Those obtained results are in compliance with the results of other studies.

In his study Ben Temime (17) examined 90 cases of molar pregnancy and noticed that β HCG serum levels ranged from 20000 IU/L to 40000 IU/L. Trissy (18) described a patient who was at 12th week of gestational age and who had β HCG level of 59540 IU.

Partial hydatidiform mole is associated with lower β HCG levels in comparison with complete hydatidiform mole. The Soto-Wright study (19) reported the preevacuationa β HCG level over 100000 IU/L in only 6% of patients with the partial hydatidiform mole, and Berkowitz (20) also reported in 2 (6%) patients of 30.

Czernobilski et al. (21) reported the preevacuation urinary level over 300000 IU/L in one (6%) of 17 patients with the partial hydatidifrom mole. In his study Chechia (22) reported even 91.4% of cases with β HCG level over 50000IU/L in 60 examined molar pregnancies.

β-HCG levels in molar pregnancy do not double as they should every two days but they are much higher than in a normal pregnancy. Therefore, dynamic increase of titer should be monitored during pregnancy especially in the postevacuation period.

Our results also suggest that β-HCG serum measurements are vital and reliable parameter for accurate diagnosis of hydatidiform mole. High β HCG levels were recorded in all statistically most significant pathomorphological vilous changes. Its levels as well as dynamic oscillations in serum values are the key parameters for disease severity scoring and further treatments.

The basic functional unit of placenta contains chorionic villi, finger-like projections of chorion, and terminal villi represent end branches of villous tree (23). There is epithelium (trophoblast) on the chorionic villi surface which consists of two clearly defined layers until the first trimester – syncytiotrophoblast and cytotrophoblast. Disorder in regulation of blastocyst invasion is associated with the most pathological pregnancies (24).

Partial mole appears as a mosaic of normal and pathologically changed villi, it is characterized by the existence of a mixture of various villi population consisting of morphologically normal villi and edematous ones of irregular shape that have cisterns and trophoblastic hyperplasia (7). Molar pregnancy is characterized by various degree of hyperplasia and anaplasia of chorionic epithelium (25). Trophoblast proliferation was present in all examined mole. Mild trophoblast proliferation typically matching a gestational age was noticed in a normal pregnancy. However, it was not considered to be pathological.

Abnormal, nonpolar trophoblast hyperplasia was present in molar pregnancy and it was almost always local and less pronounced then in complete mole. It was usually multifocal rather than circumferential showing a lace-like patter or vacuolar appearance resembling cell cavities (7). Presence of trophoblast proliferation in partial mole was suggested by numerous authors (7,12,26).

Unlike a normal pregnancy, presence of trophoblast atypia was observed in all cases with partial mole. Mild atypia was statistically most significant (57.14%) in comparison with moderate (28.57%) and pronounced (14.29%). Montes (27) in his study on trophoblast atypia incidence reported the focal atypia in 5% cases out of 22 spontaneously aborted pregnancies, predominantly focal in 40% of 30 partial mole out of which 33% moderate and 7% pronounced, and predominantly diffuse in 87% of 47 cases of complete mole.

Abnormal trophoblast hyperplasia is a requirement for the diagnosis of molar pregnancy (7). An atypical patter of trophoblast hyperplasia with peripheral or multifocal pattern rather than the polar accentuation seen in a normal first trimester placenta seems to be the important diagnostic feature for partial mole (28).

Examining trophoblast proliferation mass in our study, we noticed that the pronounced one prevailed in 45.71% of cases, while moderate and mild were observed in 28.57% and 25.71% of cases respectively. The amount of villi affected by trophoblast proliferation was the most significant in moderate (51.43%).

Salafia (29) reported the highest percentage of moderate mass and amount of trophoblast proliferation. Of 20 examined partial mole, Jaffar (30) reported focal and diffuse trophoblast proliferation in 75% and 15% cases respectively.

The results on the presence of variability of villous trophoblast were also reported by the authors (26,31). The presence of three types of trophoblast proliferation in molar pregnancy was suggested by Ishikawa (32).

There are great differences in mass and amount of trophoblast proliferation atypia in certain pathological pregnancies. Supporting the idea, Park and Lees in 1950 quoted: "Morphologically, trophoblast with benign future is completely similar to trophoblast with malignant future" (25). Therefore, the material obtained by curettage after the molar tissue has been evacuated is of a great importance in diagnostics. The tissue is the most significant evidence of the extent to which the chorionic epithelium invaded a wall of the uterus and blood vessels indicating damaging effects as well as clinical potential of mole (25).

Hydatidiform mole with pronounced trophoblastic cells hyperplasia indicates to a precancerous condition, i.e. a state associated with a significantly increased risk of cancer. Choriocarcinoma occurs to ten times more frequently after the pregnancy with hydatidiform mole then in normal pregnancy (1). Risk of developing cancer is six times lesser with

partial mole then it is seen with complete mole (10). Since we recognized the typical microscopic trophoblast characteristics of molar pregnancy according to (12), it can be concluded that the pathomorphologic analysis of evacuated tissue is a reliable indicator as well as a gold standard for partial mole diagnostics.

CONCLUSION

β-HCG level measurements and pathomorphological analysis of trophoblast changed villi are significant in diagnosis of early disease stages enabling making the right treatment decisions as well as reducing morbidity and mortality.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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